REMARKS

Applicants have amended the claims to more particularly define the invention taking into consideration the outstanding Official Action. Claim 2 has been amended to recite that the low volatility component is "present in the formulation at a concentration of 0.5 to 3% w/w". Basis for the statement is found on page 5, lines 20-21 of the specification. Claim 7 has been canceled without prejudice or disclaimer. Claims 28, 32 and 39 were canceled in the preliminary amendment filed July 31, 2003. Accordingly, the claims now remaining in the application are 1-6, 8-27, 29-31 and 33-38. Applicants most respectfully submit that all the claims now present in the application are in full compliance with 35 U.S.C. §112 and are clearly patentable over the references of record.

The rejection of claims 1-39 under 35 U.S.C. §103(a) as being unpatentable over Davis et al. in view of Weers et al. has been carefully considered but is most respectfully traversed.

Applicants wish to direct the Examiner's attention to the basic requirements of a prima facie case of obviousness as set forth in the MPEP § 2143. This section states that to establish a prima facie case of obviousness, three basic criteria first must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Section 2143.03 states that all claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Applicants also most respectfully direct the Examiner's attention to MPEP § 2144.08 (page 2100-114) wherein it is stated that Office personnel should consider all rebuttal argument and evidence present by applicant and the citation of In re Soni for error in not considering evidence presented in the specification.

Davis et al. differs in several ways from claim 1 and claims dependent thereon of the present application. As would be appreciated by one of ordinary skill in the art, Davis et al. relates to aqueous systems in a nebulizer and relates to the delivery of aqueous droplets containing drug from the nebulizer. The presently claimed invention relates to non-aqueous hydrofluoroalkane (HFA) propellant systems in a metered dose inhaler and relates to the delivery of fine particles of medicament. The properties of water and HFA propellants are very different, and a person of ordinary skill in the art would not expect observations of properties in an aqueous system to be applicable to a non-aqueous HFA system. These differences alone would not provide the necessary motivation to modify the Davis et al reference to arrive at the presently claimed invention as it would be understood by one of ordinary skill in the art to which the invention pertains.

Further, a nebulizer operates in a different way from a metered dose inhaler (MDI). A nebulizer is a mechanical device which provides a source of energy, for example, in the form of ultrasonic vibration or air pressure to create **aqueous** droplets of a suitable size for inhalation. In contrast, an MDI comprises an enclosed canister in which liquefied propellant is held under pressure which, in the case of Propellant HFA 134a, is 5 to 6 bar. The nebulizer operates by providing a mechanical means of converting progressively an aqueous-based solution or suspension of medicament into

aqueous droplets, while an MDI operates by delivering a metered volume of liquefied propellant containing medicament from within the canister via an atomising orifice. The rapid expansion of the propellant through the atomising orifice provides the energy to produce an aerosol of drug particles of a suitable size for inhalation. The properties of the formulations within these systems are therefore required to be quite different as would be appreciated by one of ordinary skill in the art.

For example, a solution or suspension for nebulization will be aqueous-based, the surface tension and viscosity of which are appropriate to facilitate the formulation of aqueous droplets. In the case of an MDI, the drug is either dissolved or suspended in liquefied propellant, the polarity and vapour pressure of which is important in the effective aerosolisation of the formulation on release via the metering valve. Again, a person of ordinary skill would not apply teachings relating to a nebulizer to an MDI and the necessary motivation to modify the teachings of the prior art are not present and a prima facie case of obviousness has not be established by the combination of references. Applicants' specification may not be used to provide this teaching. In re Fritch, 23 USPQ 1780, 1784(Fed Cir. 1992) ("It is impermissible to engage in hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps.).

The drug referred to in Davis et al. is flunisolide; fluticasone propionate is not disclosed.

The technology discussed in Weers et al. relates to suspension formulations comprising a suspension medium having dispersed therein a plurality of perforated microstructures and the suspension medium permeates the perforated microstructures. The claims of the present application relate to a solution formulation, and are not directed to perforated microstructures. Teachings of the Weers et al. document would not be applied to a solution formulation such as that of the present application as would be appreciated by one of ordinary skill in the art to which the invention pertains and the necessary motivation is not present for the reasons noted above.

Weers et al. states that exemplary medicines for use in relation to that invention may be selected from a wide range of compounds of various types. Included within that list of compounds are anti-inflammatories, of which eleven are named. From that length of list of compounds it cannot be reasonably argued that it would have been obvious to the person skilled in the art to substitute flunisolide for fluticasone propionate.

Further, the person skilled in the art would know that one cannot simply substitute one anti-inflammatory compound for another. It is well known by those skilled in the art that different anti-inflammatory compounds have different physical and chemical properties, for example, they will have different densities, solubilities in propellant, solubilities in cosolvents, solubilities in water, and different chemical stabilities in solution. It would not have been obvious to a person of ordinary skill in the art to substitute flunisolide for fluticasone propionate and this aspect of the rejection should be withdrawn.

In claim 2, the low volatility component is present in the formulation at a concentration of 0.5 to 3% w/w.

In the propylene glycol-ethanol-water systems described in Davis et al., propylene glycol and ethanol are primarily used as cosolvents to promote the solubilisation of the medicament. The droplets leaving the nebulizer and subsequently inhaled by the patient comprise a mixture of water, propylene glycol and ethanol in which a drug is dissolved. In Davis et al.,, it is stated that "the mass median diameter (of droplets) increases...as the percentage of propylene glycol is decreased" (page 89).

In the MDI of the present invention a solubilising agent, in one embodiment ethanol, is primarily used as a cosolvent to solubilise the medicament which, together with the HFA propellant, rapidly evaporates from the aerosol droplets initially expelled from the MDI, so that the particles inhaled largely comprise low volatility component and drug (the drug is likely to be dissolved in the low volatility component, in one embodiment propylene glycol). The low volatility component serves to maintain the desired size of particle which comprises the low volatility component and drug so that the fine particle mass, as defined by the content of stages 3-5 of an Andersen Cascade

Impactor, matches better the distribution of the drug particles delivered by the then existing commercialised suspension formulations which contained CFCs (see page 5, lines 3-11). Davis et al. does not address the problem of a particle size distribution which have a higher content of finer particles so that the distribution does not match that of commercialised CFC formulations which can lead to a higher systemic exposure to the aerosol particles due to deep lung penetration which can enhance the undesired systemic effects of drugs.

The fact that the function of the propylene glycol in Davis et al. and the low volatility component in the present application are quite different is further evidenced since the amount of propylene glycol in the formulations in Davis et al. is in the range 25 to 50% v/v (see Table 2 on page 92). In claim 2 of the present application, the concentration of the low volatility component is in the range 0.5 to 3% w/w and there is no motivation to arrive at this concentration which is a claim limitation which cannot be ignored.

From the preceding arguments it can be concluded that claims 1-27, 29-31 and 33-38, as amended, are patentable over Davis et al., in view of Weers et al. and the rejection should be withdrawn.

The rejection of claims 1-39 under 35 U.S.C. §103(a) as being unpatentable over Otterbeck et al. in view of Weers et al. has been carefully considered but is most respectfully traversed in view of the discussion above and the following comments.

Otterbeck et al. differs in several ways from the amended claims of the presently claimed invention. Otterbeck et al. discloses budesonide solutions for use as the active ingredient in rectal enemas or rectal foams. The present invention relates to HFA propellant systems in a metered dose inhaler to deliver fine particles of medicament to the lungs.

HFA propellant systems are not disclosed in Otterbeck et al. In Otterbeck et al. it is stated that "the propellant gases preferably used are ... hydrocarbons such as isobutene, n-butane or propane/n-butane mixtures". (column 4, lines 19-21.)

None of the Examples in Otterbeck et al. teach the combination of a low volatility component, fro example propylene glycol and ethanol, the Examples teach the addition of propylene glycol or ethanol. In Otterbeck et al. it is stated that "The alcohols used for the purposes of the present invention are preferably propylene glycol, ethanol or isopropanol." (Column 3, lines 36-37.)

In the present invention, as stated above, the low volatility component is added to maintain the desired particle size, however in Otterbeck et al. particle size is not important as the solution is for a different use and a low volatility component is not added for the purpose of maintaining particle size.

Propylene glycol is added merely as a solubilising agent in Otterbeck et al. and the differing function is further evidenced since propylene glycol is added in such large amounts, in Otterbeck et al. 35g in Examples 7, 8 and 9 when budesonide is present at only 0.0182g. The concentration of the low volatility component in claim 2 of the present invention is typically in the range of 0.5-3% w/w.

The drug referred to in Otterbeck et al. is budesonide; fluticasone propionate is not disclosed in Otterbeck et al.

As previously stated, the person skilled in the art would know that one cannot simply substitute one anti-inflammatory compound for another, it would not have been obvious to one skilled in the art to substitute budesonide with fluticasone propionate. It is well known by those skilled in the art that different anti-inflammatory compounds have different physical and chemical properties, for example, they will have different densities, solubilities in propellant, solubilities in cosolvents, solubilities in water, and different chemical stabilities in solution. Accordingly, it is most respectfully requested that this rejection be withdrawn.

In view of the above comments and further amendments to the claims, favorable reconsideration and allowance of all of the claims now present in the application are most respectfully requested.

Respectfully submitted,

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